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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KRASS, FREDERICK F	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	10/771,259	HARMENBERG ET AL.	
	Examiner	Art Unit	
	Frederick F. Krass	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) ____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Reissue Oath is Defective

Claims 1-40 are rejected under 35 U.S.C. § 251 as relying upon a defective reissue oath/declaration.

The reissue oath/declaration filed with this application is defective because it fails to identify at least one error which is relied upon to support the reissue application. See 37 CFR 1.175(a)(1) and MPEP § 1414. The statement at the tope of page 2 of the oath that "Claim 1 is too broad" is merely a non-specific conclusion, not a statement of a specific error.

Scope of Enablement Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3 and 16-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for i) synergistic combinations of specific antiviral agents and specific glucocorticoids, and ii) the treatment of individuals identified to be at risk to develop herpes, does not reasonably provide enablement for iii) synergistic combinations of functionally defined antivirals and specific glucocorticoids and iv) "prophylaxis" of herpes infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1. The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art

The invention relates to synergistic combinations of particular antiviral agents and glucocorticoids, and the treatment of herpes infections with same. The relative skill of those in the art is high, that of an MD or PHD. While the relative skill of those in the art is high, this is outweighed by the highly unpredictable nature of the invention. Specifically, "synergy", i.e. a greater than additive effect for a given particular combination as compared to the individual agents in that combination when used alone, is generally unpredictable in the fields of medicine and biochemistry, and particularly so in the case of treating viral infections. See, only as exemplary of the current state of the art in this regard, USP 5,856,364 at col. 5, lines 56-65 and col. 20, lines 56-61; see also USP 4,902,678 at col. 2, lines 29-32 and col. 3, lines 35-66. (Note especially the speculative language used by the latter reference regarding the predictability of synergy). Thus, the ability of any given combination of agents for herpes treatment to exhibit synergy cannot be predicted *a priori*, and must be determined empirically on a case-by-case basis.

Similarly, the "prophylaxis" of herpes infections is highly unpredictable. While one can identify patients at risk to develop herpes, e.g. those having had previous infections, or who are sexually involved with infected individuals, and then treat such individuals to reduce their risk, one cannot simply prevent all herpes outbreaks in a blanket manner as implied by the broad term "prophylaxis". No specific regimens or

protocols for achieving such blanket prevention are reasonably set forth by the specification as originally filed.

2. The breadth of the claims

The rejected claims are broad and inclusive of i) combinations of antivirals characterized only by function (those that are "herpes-specific" and "preferentially phosphorylated in virus-infected cells") with glucocorticoids and ii) "prophylaxis" broadly.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no guidance for selecting synergistic combinations comprising unspecified, functionally characterized antiviral agents with glucocorticoids. The working examples disclose and test only specified combinations, e.g. foscarnet and budesonide, foscarnet and hydrocortisone, acyclovir and hydrocortisone, etc. The specification also provides no example of complete prevention, i.e. non-specific "prophylaxis".

4. The quantity of experimentation necessary

Applicant fails to provide information allowing the skilled artisan to ascertain which unspecified, functionally characterized antiviral agents can reasonably be expected to function synergistically. In the instant case, only a limited number of combinations are exemplified in the working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The instant claims are broad and read on an overwhelming number of possible combinations, necessitating an exhaustive and undue search for all the embodiments suitable to practice the claimed invention. Given the sheer number of potential combinations and the recognized unpredictability of this art one would have

to mount a massive additional research campaign to determine which combinations, where the antiviral agent is not specifically named but rather characterized only by function, would exhibit the synergy required by the instant claims. Accordingly, applicant has failed to provide information sufficient to practice the claimed invention absent resorting to undue experimentation.

Similarly, no guidance is provided for "prophylaxis" broadly. The rejection of claims 17-36, 38 and 40 on this basis can be obviated by changing the language of the first few lines of claims 17, 18 and 24 to read as follows:

--- A method for treating herpes virus infections of the skin or mucous membranes in mammals having or identified to be at risk of developing said infections, comprising topically administering thereto, in combination... ----

Indefiniteness Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-16, 24, 25 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claimed percentage values recited by the instantly rejected claims are unclear because they do not include the basis for the measurement, e.g. percent by weight based on the total weight of the composition, percent by volume based on the total volume of the carrier, etc. See Honeywell Intl., Inc. v. Intl. Trade Commn., 341 F.3d 1332, 1340 (Fed. Cir. 2003). (Holding that, where a claimed value varies with its method of measurement and several alternative methods of measurement are available, the claimed value is indefinite where the method of measurement is not also specified).

Obviousness Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1) Claims 1-4, 7, 13-21 and 23-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levin (USP 5,656,301).

The prior art discloses synergistic compositions comprising 1) LYCD and 0.5 percent acyclovir (col. 8, lines 51-57) or 2) LYCD and 0.5 percent hydrocortisone (col. 11, lines 27-42). The latter

compositions are applied topically (as ointments) to the sites of (recurrent) herpes infection (face and neck), 2 to 4 times daily. See example 32, spanning columns 11 and 12.

LYCD is not excluded from the instant claims by the intermediate transitional phrase "consisting essentially of" since it does not materially affect the basic and novel characteristics of the claimed invention, i.e. the prior art compositions remain useful for treating herpes infections after LYCD is included. Accordingly, the prior art differs from the instant claims insofar as it does not disclose the use of acyclovir and hydrocortisone simulataneously.

Established precedent has long held that it is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 USPQ 186, 188 (CCPA 1960). Accordingly, it would have been obvious to have combined topical compositions "1)" and "2)", disclosed by the prior art at col. 8, lines 51-57 and col. 11, lines 27-42, both useful for the topical treatment of herpes infections, to form a third composition to be used for that very same purpose, motivated by the sound reasoning provided by such precedent. Regarding dependent claims 14 and 15, it would also have been obvious to have varied the relative proportions of each agent to optimize performance, e.g. to increase the amount of acylovir to intensify its expected antiviral effect.

2) Claims 1-5, 7-10, 13-21 and 23-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (USP 4,902,678) in view of Underwood (USP 3,317,384).

The primary reference discloses synergistic combinations of foscarnet and acyclovir. See col. 1, lines 67 and 68 and col. 2, line 49. See also col. 2, lines 29-32, and the working examples. These combinations are administered two to four times a day to infected sites as topical compositions (ointments or creams) comprising 1-5 weight percent of each drug to treat herpes infections. See col. 4, lines 31-45. (As is well-known, herpes infections are recurrent: see col. 1, lines 42-45, for example). Furthermore, the relative proportions and dosages may be varied in order to optimize performance, as taught at col. 2,

lines 1-5. (Although optical administration is discussed at col. 4, lines 31-35, it is clear from the overall context of the prior art disclosure that topical administration to skin is reasonably contemplated. See for example the discussion of col. 1, lines 17-60; col. 2, lines 13-30; and col. 11, lines 6-14. Where a particular herpes strain manifested itself on the skin of the head and neck, for example, it would have been obvious, in a self-evident manner, to have administered the topical compositions to those infected sites.)

The primary reference thus differs substantially from the instant claims insofar as it is silent regarding the use of a glucocorticoid. It is well-known, however, to use a glucocorticoid to decrease side effects associated with topical antiviral nucleosides when treating herpes infections. See col. 1, lines 32-39. (Note that the secondary reference also recognizes the equivalency of treating ocular and skin infections therein, consistent with the state of the art). Specified glucocorticoids include hydrocortisone (col. 1, line 52). The percentage of glucocorticoid used ranges from about 0.025 to about 2.5 percent (col. 2, lines 14-20).

The secondary reference differs from the instant claims insofar as it does not specifically disclose the use of one of the specific instantly claimed antiviral agents, e.g. acyclovir. It does, however, suggest the use of antiviral compounds generally at col. 1, lines 55-57, stating there that useful antiviral nucleosides include those "demonstrating beneficial activity in the treatment of viral ophthalmic conditions and viral skin lesions." Acyclovir is clearly a compound of this general type. Accordingly, it would have been obvious to have incorporated a glucocorticoid such as hydrocortisone into the primary reference compositions, motivated by the desire to provide improved therapeutic efficacy (itself another type of "synergy") by reducing side effects as taught by the secondary reference.

3) Claims 6, 11, 12 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (USP 4,902,678) in view of Underwood (USP 3,317,384), further in view of Chemical Abstract 103:172328.

The primary and secondary references, and the rationale for combining their teachings, is detailed in subsection "2)" supra. The antiviral compositions and treatments suggested by their combined

teachings differ from the instant claims insofar as they do not include the specific glucocorticoid budesonide.

The secondary reference clearly teaches that useful glucocorticoids include "steroids of natural and synthetic origin which demonstrate topical anti-inflammatory properties." (Col. 1, lines 46-48). Budesonide is just such a compound, as illustrated by the tertiary reference. Moreover, the latter reference teaches that budesonide is superior to conventional steroids, such as hydrocortisone, because it has higher anti-inflammatory activity and lower side effects. (The tertiary reference relates to a specific laboratory study, and thus differs from the instant claims in that it is silent regarding antiviral compounds). Accordingly, it would have been obvious to have used budesonide as the glucocorticoid of the compositions suggested by the combined teachings of the primary and secondary references, motivated by the desire to provide improved anti-inflammatory activity while lowering side effects as taught by the tertiary reference.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick F. Krass whose telephone number is 571-272-0580. The examiner's schedule is as follows:

Monday: 10:30AM- 7PM;
Tuesday: 10:30AM - 7PM;
Wednesday: off;
Thursday: 10:30AM- 7PM; and
Friday: 10:30AM-7PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

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Frederick Krass
Primary Examiner
Art Unit 1614